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(54) Title: SAMPLING AND ANALYSIS OF REACTIONS BY TRAPPING REACTION COMPONENTS ON A SORBENT (57) Abstract Methods and devices for rapidly analyzing groups of reactions are disclosed. The method includes the steps of contacting a fluid sample from one of the reaction mixtures with a sorbent, trapping at least one component of the fluid sample on the sorbent, and detecting the at least one component of the fluid sample trapped on the sorbent. The contacting step, the trapping step, and the detecting step are carried out at least once for each of the reaction mixtures in rapid serial or parallel fashion. The present invention is useful for screening combinatorial libraries, especially libraries of catalysts made through parallel synthesis, but the disclosed methods and devices can be used to analyze a broad spectrum of chemical transformations.		

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**SAMPLING AND ANALYSIS OF REACTIONS BY TRAPPING REACTION
COMPONENTS ON A SORBENT**

BACKGROUND OF THE INVENTION

5 Technical Field

The present invention relates to a method and apparatus for analyzing reaction mixtures, and relates more particularly, to a method and apparatus for screening combinatorial libraries.

10 Discussion

Combinatorial chemistry refers generally to methods for rapidly creating—vast collections of compounds having diverse structures—and to methods for rapidly testing or screening chemical libraries to identify and optimize structures exhibiting desired properties.

15 Combinatorial chemistry is an effective research strategy for discovering useful materials. For example, pharmaceutical scientists have successfully used such techniques to dramatically increase the speed of drug discovery. Material scientists have employed combinatorial methods to develop novel high temperature superconductors, magnetoresistive materials, and phosphors. More recently,
20 scientists have applied combinatorial methods to develop catalysts. See, for example, co-pending U.S. patent application no. 08/327,513 "The Combinatorial Synthesis of Novel Materials" (published as WO 96/11878) and co-pending U.S. patent application no. 08/898,715 "Combinatorial Synthesis and Analysis of Organometallic Compounds and Catalysts" (published as WO 98/03521), which are
25 both herein incorporated by reference.

Combinatorial libraries may consist of molecules free in solution, bound to solid particles, or arrayed on a solid support, and can be prepared in at least two different ways. In one method, often called split synthesis, a starting reactant is attached to a suitable solid support—polystyrene beads, for example—and the beads
30 are split into two or more groups. Each group of beads is then treated with different

reagents or molecular building blocks. Once treated, the groups of beads are pooled, mixed, and split again into several groups. Each group of beads is then treated with different reagents from a second set of reagents that build on the compounds from the previous treatment step. The splitting, treating and pooling steps can be repeated
5 many times with different sets of reagents resulting in a combinatorial library comprised of a large number of structurally diverse member compounds, each immobilized on discrete solid supports.

In another method, often called parallel synthesis, individual library members are synthesized in separate vessels, or arrayed on planar solid supports (wafers)
10 frequently using automated dispensing instruments. Each vessel or wafer array position is provided with a starting reactant, which is treated with different reactants or molecular building blocks. The treating step can be repeated many times with different sets of reagents resulting in a structurally diverse combinatorial library. Generally, split synthesis produces small quantities of a relatively large number of
15 compounds, while parallel synthesis produces larger quantities of a relatively small number of compounds. But, even with parallel synthesis the quantity of each library member is typically only a few micrograms.

Though when compared to traditional approaches, new and useful materials can be developed in less time using combinatorial methods, further efficiency gains
20 can be achieved by improving library screening. Once a researcher creates a combinatorial library, he or she faces the daunting task of identifying a handful of promising materials out of a combinatorial library comprising hundreds, thousands or perhaps millions of compounds. Generally, the speed at which one may screen libraries for useful properties has not kept pace with the speed at which libraries can
25 be created.

Furthermore, screening library members for catalytic activity presents unique problems. For example, screening methods developed for solid phase catalysts are often unsuitable for use with solution phase catalysts. Furthermore, many screening methods developed for solution-phase catalysts, which rely on quantifying the
30 amount of a desired product formed by contacting reactants with the catalysts,

on the sorbent. The contacting step, the trapping step, and the detecting step are carried out at least once for each of the reaction mixtures.

In accordance with a third aspect of the present invention, there is provided an apparatus for analyzing reaction mixtures. The apparatus comprises a reaction
5 block having wells formed along an upper surface, and a sorbent layer disposed above the upper surface of the reaction block such that the wells and the sorbent layer define vessels for containing the reaction mixtures. The sorbent layer is adapted to trap at least one fluid component of the reaction mixtures.

In accordance with a fourth aspect of the present invention, there is provided
10 an apparatus for analyzing reaction mixtures comprising vessels for containing each of the reaction mixtures, and discrete sorbent traps that are in fluid communication with the vessels. The sorbent traps are adapted to trap at least one fluid component of the reaction mixtures.

In accordance with a fifth aspect of the present invention, there is provided
15 an apparatus for screening reaction mixtures in which at least one constituent of the reaction mixtures is contained in depressions located along a top surface of a planar substrate. The apparatus comprises a heating block that is adapted to support the planar substrate and to provide thermal contact with a bottom surface of the planar substrate. The apparatus includes a gas permeable sorbent layer having an upper
20 surface and a lower surface, in which the lower surface of the sorbent layer is disposed above the top surface of the planar substrate. The sorbent layer is adapted to trap at least one vapor phase component of the reaction mixtures. The apparatus further comprise a cover having an upper surface and a lower surface, the lower surface of the reactor cover disposed above the upper surface of the sorbent layer.
25 Passageways are formed in the cover that extend from the lower to the upper surfaces of the cover and provide flow paths for vapor phase components of the reaction mixtures from the upper surface of the cover to the at least one constituent of the reactive mixture.

Fig. 1 is a flow chart illustrating the general features of the disclosed method.

Fig. 2 shows a cross-sectional view of a portion of an apparatus that can be used to screen catalyst library members arrayed on a wafer.

5 Fig. 3 shows a cross-sectional view of an apparatus that can be used to analyze liquid-phase reaction mixtures.

Fig. 4 shows a cross-sectional view of an apparatus that can be used to analyze reaction mixtures, especially those comprising catalyst library members.

10 Fig. 5 shows a cross-sectional view of a portion of an apparatus that can be used to screen catalyst library members with both gas-phase and liquid-phase reactants.

Fig. 6 shows a cross-sectional view of a portion of an apparatus that can be used to screen catalyst library members with gas-phase reactants.

15 Fig. 7 is a photograph of a TLC plate spotted with 2 microliter aliquots of reaction mixtures and stained with fluorescamine.

Fig. 8 shows a typical bar plot of integrated fluorescence intensity of spots on a TLC plate.

Fig. 9 shows a plot of fluorescence intensity of an aniline-fluorescamine product versus the amount of aniline.

20

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a method and apparatus for rapidly analyzing reactions. Although one may use the invention to examine a broad range of gas and liquid-phase reactions, it is especially useful for screening combinatorial libraries. As described below, an important application includes distinguishing library members based on their ability to catalyze a particular reaction.

25 Fig. 1 illustrates general features of the method 10 for analyzing reaction mixtures 12. The method comprises the steps of contacting 14 a fluid sample from one of the reaction mixtures 12 with a sorbent, followed by trapping 16 at least one
30

component of the fluid sample on the sorbent, and detecting 18 the trapped component or components. The fluid sample can be a liquid or a gas or a mixture of a gas and a liquid. Each of the reaction mixtures 12 can include, but is not limited to reactants, products, solvents, catalysts and activators. Typically, the trapped
5 component is a reaction product, but it can be any fluid component of the reaction mixture, including a reactant. To speed analysis, the contacting 14 step or the detecting 18 step or both can be carried out for two or more of the reaction mixtures 12 simultaneously (that is, in parallel). Normally, fluid samples from each of the reaction mixtures 12 are in contact with the sorbents for the same amount time.

10 Sorbent contacting 14 can occur through many methods. For example, after loading reaction mixtures 12 in vessels, individual sorbent traps can be placed in the headspace of each of the vessels, so that during reaction the vapor phase of each of the reaction mixtures contacts the sorbent. Alternatively, the sorbent traps may be located outside of the vessels, but in fluid communication with the headspace of the
15 vessels via conduits. In either case, if the reaction mixtures comprise a liquid phase and a vapor phase, the fraction of the component of interest in the vapor phase is generally different than the fraction of the same component in the liquid phase. This may lead to difficulties in comparing data among reaction mixtures. To minimize this problem, the reaction mixtures can be completely vaporized at the conclusion of
20 reaction by heating or by applying vacuum or by heating and applying vacuum at the same time.

Instead of individual traps, the sorbent may consist of a thin layer of sorbent. In such cases, the reaction mixtures 12 can be placed in vessels formed in a surface of a reaction block. One may then place the layer of sorbent on the surface of the
25 reaction block so that vapor from each of the reaction mixtures contacts discrete areas of the sorbent layer during or following reaction. The sorbent layer may be disposed on a solid substrate, e.g., thin layer chromatography (TLC) plate, and may be discontinuous to help prevent component migration from one of the discrete contacting areas to another. Furthermore, the solid substrate can be gas permeable,
30 allowing vapor from each of the reaction mixtures to pass through the sorbent layer.

The gas permeable substrate is useful when analyzing gas-phase reactions—one may charge (pressurize) each of the vessels with one or more gaseous reactants, and then vent the mixture through the sorbent layer following reaction, trapping the desired component.

5 When the fluid samples are liquids, one may use standard liquid transfer techniques for sorbent contacting. For example, a pipette or similar device can be used to withdraw a predetermined amount of fluid sample from a reaction mixture, and to apply the fluid sample on the sorbent. A multiple-tipped pipette, which is used to deliver liquid reagents to standard 96-well microtiter plates, can be used to
10 transfer fluid samples, either manually or automatically, from multiple reaction mixtures simultaneously. Because the volume of each fluid sample is small—a few microliters, say—fluid samples from numerous reaction mixtures can be applied to discrete locations on a sorbent layer, similar to “spotting” on TLC plates.

 The choice of sorbent depends on the nature of the trapped component
15 including the component's size, polarity, charge, solubility in the fluid sample, and chemical structure. Useful sorbents generally include finely divided or microporous adsorbents used in solid phase extraction (SPE), liquid chromatography (adsorption and ionic exchange chromatography), and TLC. These materials include, but are not limited to, silica—with or without a bonded phase—activated alumina, magnesium
20 silicate, graphitized carbon, dextran, agarose, cellulose, methacrylate, polystyrene, and divinylbenzene-polystyrene copolymer. Typical groups that comprise the silica bonded phase include butyldimethyl, octyl, octadecyl, cyanopropyl, diol, aminopropyl, phenyl, and phenyl polysiloxane. Other suitable sorbents include affinity chromatography media, which comprise a support matrix—cross-linked
25 agarose, cellulose, or modified methacrylate, for instance—and ligands linked to the matrix. The ligands exhibit specific and reversible binding affinity for the trapped component. In some cases, spacer arms link small ligands to the matrix to improve bonding with the trapped component.

 Trapping 16 can occur through physical adsorption, chemisorption,
30 absorption, or chemical bonding. The trapping mechanism depends on the chemical

structure of the sorbent and the component, and can strongly influence the detecting 18 step. For example, certain detection techniques, such as gas chromatography, mass spectroscopy, and liquid chromatography, require the release of the component from the sorbent. Such detection techniques would preclude the use of a sorbent that, 5 for example, irreversibly bonds to the component. Furthermore, choosing a sorbent that is highly selective for the component can improve the accuracy of the detecting 18 step by reducing interference from other constituents of the fluid sample.

The detecting 18 step may be quantitative, yielding an absolute measure of the amount of the trapped component. By repeating the contacting 14 step, the 10 trapping 16 step, and the detecting 18 step during the course of reaction, one may determine rates of reaction from changes in the amount of the trapped component with time. Instead of quantitative data, the detecting 18 step may provide qualitative data, which one can use to rank reaction mixtures 12.

In many cases, the component or components are detected while trapped on 15 the sorbent. In one approach, the trapped component is detected by absorption spectroscopy, which involves measuring the absorption of radiant energy by the trapped component. Absorption can occur throughout the electromagnetic spectrum, ranging from the gamma region (nuclear resonance absorption) to the radio region (nuclear magnetic resonance), though generally absorption spectroscopy is 20 performed in the ultraviolet, visible, and infrared regions of the electromagnetic spectrum. Through appropriate calibration, the absorption spectrum can be used to quantify the amount of the component trapped on the sorbent.

In another approach, the sorbent is exposed to one or more indicator reagents to obtain a characteristic change in appearance of the sorbent resulting from an 25 interaction or reaction of the indicator reagent with the trapped sorbent. Changes in appearance of the sorbent include changes in color that are visible to the eye or changes in fluorescence when the sorbent is exposed to ultraviolet light. Suitable indicator reagents (stains) include those used to visualize TLC spots. Table 1 lists some useful reagents for detecting various classes of components sampled from the 30 reactions mixtures 12.

Table 1. Indicator Reagents for Detection of Reaction Mixture Components.

Component Class	Indicator Reagent
Acetylene	Dicobalt octacarbonyl
Acid, organic	Bromocresol green Bromocresol green-bromophenol blue-potassium permanganate Bromocresol purple Glucose-Aniline
Acid, organic aromatic	Hydrogen Peroxide
Alcohols, higher, phenols	Vanillin-sulphuric acid
Aldehydes, Ketones	o-Diansidine 4-Amino-5-hydrazino-1,2,4-triazole-3-thiol biphenyl-2-amine 2,4-Dinitrophenylhydrazine Malachite green Phosphomolybdic acid
Amides	Chlorine-pyrazolinone-cyanide Hydroxylamine-ferric chloride
Amines, aliphatic	Nitroprusside(sodium)-acetaldehyde Nitroprusside(sodium)-ferricyanide 1-Naphthaleneacetic anhydride
Amines, primary	Ninhydrin Fluorescamine
Amines, secondary	Dansyl chloride
Amines, aromatic	Sodium nitrite-HCl-a-naphthol 5-Chloro-4,6-dinitrobenzofuran 2,6-dibromo-4-quinonechlorimine (Gibb's Reagent)
Amino acids	2,4-Dinitrofluorobenzene Isatin-zinc acetate
Anhydrides	Hydroxylamine-ferric chloride
Coumarins	Cupric sulphate-citrate
1,2-Diols	Lead tetraacetate Lead tetraacetate-rosaniline
Disulphides	Nitroprusside (sodium)
Esters	Hydroxylamine-ferric chloride
Heterocycles, N-containing	4-Methylumbelliferone Tetracyanoethylene
Indole and derivatives	Cinnamaldehyde-HCl 4-Dimethylaminobenzaldehyde-HCl 4-Dimethylaminocinnamaldehyde Ferric chloride-perchloric acid Ferric chloride-sulphuric acid
Keto acids	o-Phenylenediamine-trichloroacetic acid

Component Class	Indicator Reagent
Ketones, methyl	Nitroprusside(sodium)-NaOH
Lactones	Hydroxylamine-ferric chloride
Mercaptans	Nitroprusside(sodium)
Quaternary ammonium salts	Dragendorff's reagent
Oximes	Cupric chloride
Phthalate esters	Resorcinol-zinc chloride-sulphuric acid
Polyalcohols	Silver nitrate-sodium hydroxide Potassium permanganate Metaperiodate(sodium)-benzidine
Polyethylene glycols and derivatives	Iodine-sulphuric acid
Polyphenols	Stannic chloride
Polyphenyls	Cerium sulphate-nitric acid
Pyridine compounds	Chlorine-pyrazolinone-cyanide Bromine cyanide-4-aminobenzoic acid
Pyrimidines, barbiturates	Fluorescein-ammonia
Sulphonic acid, alkyl and aryl	Pinacryptol yellow Silver nitrate-fluorescein
Terpenes	Antimony chloride
Urea and derivatives	Nitroprusside(sodium)-hydrogen peroxide
Xanthine derivatives	Ferric chloride-iodine

For screening purposes, a visual comparison of stained sorbents is often sufficient to rank reaction mixtures. But, the use of indicator reagents along with devices for measuring color intensity—a charged couple device (CCD) camera or a spectrum analyzer, for example—can provide accurate quantitative as well as precise qualitative information about the reaction mixtures 12. Thus, a CCD camera, for instance, can distinguish between sorbent stains that appear similar to the unaided eye. Through proper calibration with standards, the CCD camera can also yield an absolute measure of the amount of the trapped component on the sorbent. One can use the quantitative data to calculate conversion, rates of reaction, catalyst selectivity, and the like.

As mentioned above, gas chromatography, liquid chromatography, and mass spectroscopy, can be used in the detecting 18 step, but require removal of the trapped component from the sorbent (adsorption spectroscopy, including nuclear magnetic resonance spectroscopy, can also be used to detect the component after removal from the sorbent). The method for removing the trapped component depends on the nature

of the trapping mechanism, but typically includes heating the sorbent (thermal desorption) or washing the sorbent with a solvent, or a combination of thermal desorption and solvent washing. The solvent can be a gas or a liquid, and should exhibit a greater affinity for the trapped component than the sorbent at the removal
5 temperature.

Although the disclosed method can be used to study a broad range of gas and liquid-phase reactions, it is especially useful for screening catalyst libraries. Unless otherwise clear from its context, the term "catalyst" is used interchangeably to refer to metal complexes or pre-catalysts before activation, and to active catalyst species
10 themselves. Also, the catalyst may not be an isolated complex, but instead may be a mixture of a ligand with a metal. In such cases, the ligand may be obtained from a ligand library, and later mixed with a metal or metal precursor to cause catalysis. Thus, library members can be ligands, which are not catalysts themselves, but must be at least mixed with a metal or metal precursor; library members can also be
15 metal-ligand complexes mixtures of ligands and metals or metal precursors, and the like.

The disclosed method of Fig. 1 can be readily applied to screening catalyst libraries made by parallel synthesis. Each library member is combined with one or more reactants to form the reaction mixtures 12. Each of the reaction mixtures 12
20 can further include one or more solvents, activators, and other additives needed for reaction. In an initial or primary screen, each of the reaction mixtures usually differ only in the catalyst used. Once the primary screen identifies a set of leads or promising catalysts, the reaction mixtures and conditions can be varied in a secondary screen to further characterize the promising members of the catalyst
25 library.

During or after reaction, fluid samples from each of the reaction mixtures 12 are contacted with a sorbent in order to trap at least one component of the fluid samples, which is typically a desired reaction product. Following the contacting 14 and the trapping 16 steps, the trapped component or components are detected by the
30 methods described earlier. These methods include: direct absorption spectroscopy of

the trapped component; staining the sorbent with an indicator reagent followed by fluorescence detection or colorimetric analysis; and removal of the component from the sorbent, followed by quantification using liquid chromatography, gas chromatography or mass spectroscopy.

5 Fig. 2 – Fig. 6 show useful devices for carrying out the disclosed method. Although many of the devices are described in terms of screening libraries of catalysts, the various devices can be used to analyze a broad spectrum of reaction mixtures.

10 Fig. 2 shows a cross-sectional view of a portion of an apparatus 40 that can be used to screen catalyst library members 42. The library members 42, along with other condensed-phase constituents of the reaction mixtures, are deposited in depressions 44 formed along an upper surface 46 of a planar substrate or wafer 48. A lower surface 50 of the wafer 48 is disposed on a heating block 52. Porous sorbent 54 is deposited in depressions 56 formed along an upper surface 58 of a gas permeable solid layer 60. Alternatively, the sorbent can be deposited in depressions 15 formed along a lower surface 62 of the gas permeable solid layer, or can comprise a continuous layer supported on either the upper surface 58 or the lower surface 62 of the gas permeable solid layer 60. The gas permeable solid layer 60 can comprise any inert, porous material, including glass, metal or polymer frits, quartz paper, or wire 20 mesh. Examples of polymer frits include those made from polyethylene or polytetrafluoroethylene (PTFE); "inert" means the material is chemically resistant to the specific reaction mixtures it may contact during use. One may dispense with the gas permeable solid layer 60 if the sorbent can be formed into a dimensionally stable layer.

25 As shown in Fig. 2, the gas permeable solid layer 60 is positioned above the wafer 48. An optional first gasket 64, which can be any inert, resilient material, provides stress relief, and helps prevent migration of reaction mixture components between library members 42. A cover 66, having an upper surface 68 and a lower surface 70 is disposed above the upper surface 58 of the gas permeable solid layer 30 60. An optional second gasket 72 is sandwiched between the lower surface 70 of the

cover 66, and the upper surface 58 of the gas permeable solid layer 60. Like the first gasket 64, the second gasket 72 can be any inert, resilient material, provides stress relief, and helps prevent cross contamination of reaction mixtures. Clamps 74 or similar compressive fasteners holds the various parts of the apparatus 40 in place.

5 Passageways 76 are formed in the cover 66 that extend from the lower 70 to the upper 68 surfaces of the cover 66 and provide flow paths for vapor phase components of the reaction mixtures. Thus, during screening, one or more gaseous reactants enter the apparatus 40 through the passageways 76, flow through the sorbent 54 and contact the library members 42 where they react. The heating block
10 52 provides thermal energy, if needed to drive the reactions, and is either surrounded by a temperature-controlled heating blanket or immersed in a temperature-regulated bath. Alternatively, the heating block 52 can contain heating elements and temperature sensing devices—thermocouples (TC), thermistors, resistance thermometric devices (RTD), and the like—that communicate with a processor (not
15 shown) that maintains the temperature of each of the library members 42 at one or more pre-selected values. Reaction products diffuse away from the library members 42 and contact the sorbent 54, which selectively traps one or more reaction products of interest. After the reactions are complete, one measures the relative or absolute amount of the trapped component in accordance with the detecting 18 step of Fig. 1.

20 Fig. 3 shows a cross-sectional view of an apparatus 90 that can be used to analyze liquid-phase reaction mixtures 92. The apparatus comprises a reaction block 94 having wells 96 formed along an upper surface 98 for containing the reaction mixtures 92. Optionally, each of the wells 96 can contain a removable lining 100—such as a glass insert—so that the reaction mixtures 92 can be easily removed from
25 the reaction block 94. A sorbent layer 102 is disposed above the upper surface 98 of the reaction block 94 such that the wells 96 (or removable lining 100) and the sorbent layer 102 define vessels for containing the reaction mixtures 92. Typically, the reaction block 94 contains heating elements and temperature sensing devices—TCs, thermistors, RTDs, and the like—that communicate with a processor (not
30 shown). The heating elements, temperature sensing devices, and the processor

comprise a temperature control system that maintains the temperature of each of the reaction mixtures 92 at one or more pre-selected values. Alternatively, the reaction block 94 can be surrounded by a temperature-controlled heating blanket or immersed in a temperature-regulated bath.

5 The sorbent layer 102 shown in Fig. 3 is supported on a solid layer 104 though one may dispense with the solid layer 104 if the sorbent layer 102 is dimensionally stable and has the requisite mechanical strength. In addition, the sorbent layer 102 shown in Fig. 3 is discontinuous: regions 106 exist along the solid layer 104 that lack sorbent. These bare regions 106, which are located between the
10 wells 96, help prevent cross contamination of reaction mixtures 92, and can be formed by bead blasting a TLC plate.

 Vapor from the reaction mixtures 92 fills the headspace 108 of each of the wells 96. During and/or following reaction, the vapor contacts the sorbent layer 102, trapping the component of interest. One can then measure the relative or absolute
15 amount of the trapped component in accordance with the detecting 18 step of Fig. 1. As discussed above, the fraction of the component of interest in the vapor phase is generally different than the fraction of the same component in the liquid phase, which may lead to difficulties in comparing data among reaction mixtures. To minimize this problem, the reaction mixtures 92 are usually completely vaporized at
20 the conclusion of reaction by heating the reaction block 94 thereby trapping a substantial amount of the component of interest.

 Fig. 4 shows a cross-sectional view of another apparatus 120 that can be used to analyze reaction mixtures, especially those comprising catalyst library members 122. Like the apparatus 90 shown in Fig. 3, it comprises a reaction block 124 having
25 wells 126 formed along an upper surface 128 for containing the catalysts 122. Each of the wells 126 shown in Fig. 4 contain an optional removable lining 130, a glass insert, for example, so that the catalyst library members 122 can be easily removed from the reaction block 124. A sorbent layer 132 is disposed above the upper surface 128 of the reaction block 124 such that the wells 126 (or removable lining 130) and
30 the sorbent layer 132 define vessels for containing the catalyst library members 122.

Typically, the reaction block 124 contains heating elements and temperature sensing devices—TCs, thermistors, RTDs, and the like—that communicate with a processor (not shown). The heating elements, temperature sensing devices, and the processor comprise a temperature control system that maintains the temperature of each of the catalyst library members 122 at one or more pre-selected values. Alternatively, the reaction block 124 can be surrounded by a temperature-controlled heating blanket or immersed in a temperature-regulated bath.

The sorbent layer 132 shown in Fig. 4 is supported on an optional, gas permeable solid layer 134, and is discontinuous. As mentioned when describing Fig. 3, these bare regions 136, which are located between the wells 126, help prevent migration of gas-phase reaction mixture components between adjacent catalyst library members 122, and can be formed by bead blasting a TLC plate.

The apparatus 120 further comprises a cover 138 having an upper surface 140 and a lower surface 142, which is disposed above the solid layer 134. Optional first 144 and second 146 gaskets, are sandwiched between the gas permeable solid layer 134 and either the upper surface 128 of the reaction block 124 or the lower surface 142 of the cover 138, respectively. The gaskets 144, 146, which can be made of any inert, resilient material, provide stress relief, and help prevent migration of reaction mixture components between catalyst library members 122. In addition, resilient spacers 148, located at the bottom 150 of each of the wells 126, prevent damage to the removable lining 130 due to compressive forces exerted by fasteners (not shown) used to seal the apparatus 120.

Passageways 152 formed in the cover 138 extend from the upper 140 to the lower 142 surfaces of the cover 138 and provide flow paths for vapor phase components of the reaction mixtures. Thus, when screening catalyst library members 122, one or more gaseous reactants enter the apparatus 120 through the passageways 152, flow through the gas permeable solid layer 134 and porous sorbent layer 132 and contact catalyst library members 122. Heating elements within the reaction block 124 provide thermal energy, if needed, to drive the reactions. Reaction products diffuse away from the library members 122 and contact the sorbent layer

132, which selectively traps one or more reaction products of interest. After the reactions are complete, one measures the relative or absolute amount of the trapped component in accordance with the detecting 18 step of Fig. 1.

Fig. 5 shows a cross-sectional view of a portion of an apparatus 170 that can be used to screen catalyst library members 172 with both gas-phase and liquid-phase reactants. Like the apparatus 90, 120 shown in Fig. 3 and 4, it comprises a reaction block 174 having wells 176 formed along an upper surface 178 for containing catalyst library members 172. Though not shown, each of the wells 176 can optionally contain a removable lining so that the catalyst library members 172 and other condensed-phase components of the reaction mixtures can be easily removed from the reaction block 174. Generally, the reaction block 174 contains heating elements and temperature sensing devices—TCs, thermistors, RTDs, and the like—that communicate with a processor (not shown). The heating elements, temperature sensing devices, and the processor comprise a temperature control system that maintains the temperature of each of the catalyst library members 172 at one or more pre-selected values. Alternatively, the reaction block 174 can be surrounded by a temperature-controlled heating blanket or immersed in a temperature-regulated bath.

The apparatus 170 further comprises a cover 180 having an upper surface 182 and a lower surface 184. The lower surface 184 of the cover 180 is disposed above the upper surface 178 of the reaction block 174, and along with the wells 176, define vessels 186 for containing the reaction mixtures. A gasket 188 is sandwiched between the reaction block 174 and the cover 180. The gasket 188, which can be made of any inert, resilient material, provides stress relief, and helps prevent migration of vapor-phase components of the reaction mixtures between vessels 186. Clamps 190 or similar compressive fasteners holds the various parts of the apparatus 170 in place.

First passageways 192 formed in the cover 180, extend from the upper surface 182 to the lower surface 184 of the cover 180, and provide flow paths for vapor phase components of the reaction mixtures. Each of the first passageways 192

contains a sorbent trap 194—a sorbent filled tube for trapping the component or components of interest.

Though component trapping can occur during reaction, screening of catalysts involved in condensed phase reactions usual' undertaken after reaction is complete.

5 In this way, one may obtain an absolute measure of the amount of a particular reaction product formed by completely vaporizing each of the reaction mixtures. During this vaporizing step, gas-phase components of the reaction mixtures exit the vessels 186 through the sorbent traps 194, which selectively entrap the desired reaction product. Because the sorbent traps 194 are located in the cover 180, the
10 trapped component can be analyzed by separating the cover 180 from the reaction block 174. The sorbent traps can have optional fittings 196 that provide connection to an analyzer such as a liquid chromatograph, gas chromatograph, or mass spectrometer.

The apparatus 170 may further comprise second passageways 198 that are
15 formed in the cover 180 and extend from the upper surface 182 to the lower surface 184 of the cover 180. When screening catalyst library members 172, one or more gas-phase reactants are introduced into the vessels 186 through the second passageways 198 and contact the catalyst library members 172 where they react. Gas-phase reaction products diffuse away from the catalyst library members 172,
20 and exit the vessels 186 through the first passageways 192 and sorbent traps 194. A check valve 200 in each of the second passageways 198 prevent gas-phase components from leaving the vessels 186 through the second passageways 198, and each of the sorbent traps 194 are fitted with a flow restrictor 202 which maintains a positive gauge pressure in the vessels 186.

25 Finally, Fig. 6 shows a cross-sectional view of a portion of an apparatus 220 that can be used to screen catalyst library members 222 with gas-phase reactants. Like the apparatus 170 shown in Fig. 5, the apparatus 220 comprises a reaction block 224 having wells 226 formed along an upper surface 228 for containing catalyst library members 222. Though not shown, each of the wells 226 can optionally
30 contain a removable lining so that the catalyst library members 222 and other

condensed-phase components of the reaction mixtures can be easily removed from the reaction block 224. Generally, the reaction block 224 contains heating elements and temperature sensing devices—TCs, thermistors, RTDs, and the like—that communicate with a processor (not shown). The heating elements, temperature
5 sensing devices, and the processor comprise a temperature control system that maintains the temperature of each of the catalyst library members 222 at one or more pre-selected values. Alternatively, the reaction block 224 can be surrounded by a temperature-controlled heating blanket or immersed in a temperature-regulated bath.

The apparatus 220 further comprises a cover 230 having an upper surface
10 232 and a lower surface 234. The lower surface 234 of the cover 230 is disposed above the upper surface 228 of the reaction block 224, and along with the wells 226, define vessels 236 for containing the reaction mixtures. A gasket 238, which sandwiched between the reaction block 224 and the cover 230, can be made of any inert, resilient material; the gasket 238 provides stress relief, and helps prevent
15 migration of vapor-phase components of the reaction mixtures between vessels 236. Clamps 240 or similar compressive fasteners holds the various parts of the apparatus 220 together.

First 242 and second 244 passageways are formed in the cover 230, and extend from the upper surface 232 to the lower surface 234 of the cover 230. The
20 first passageways 242, whose inlets 244 and outlets 246 are located along the upper surface 232 and the lower surface 234 of the cover 230, respectively, provide flow paths for vapor phase components entering the vessels 236. The second passageways 248, whose inlets 250 and outlets 252 are located along the lower surface 234 and the upper surface 232 of the cover 230, respectively, provide flow paths for vapor
25 phase components leaving the vessels 236. Sorbent traps 254 are attached to the outlets 252 of the second passageways 248 via connectors 256. The connectors 256 allow removal of the sorbent traps 254 after the contacting and trapping steps for remote analysis.

When screening catalyst library members 222, one or more gas-phase
30 reactants are introduced into the vessels 236 through gas reactant feed lines 258,

which are attached to the inlets 244 of the first passageways 242 using connectors 260. The gas-phase reactants contact the catalyst library members 222 and react. Gas-phase reaction products diffuse away from the catalyst library members 222, and exit the vessels 236 through the second passageways 248 and sorbent traps 254.

5 A check valve 262 in each of the gas reactant feed lines 258 prevent gas-phase components from leaving the vessels 236 through the first passageways 242, and each of the sorbent traps 254 are fitted with a flow restrictor 264 which maintains a positive gauge pressure in the vessels 236. In addition, the sorbent traps can have optional fittings 266 that provide connection to an analyzer such as a liquid

10 chromatograph, gas chromatograph, or mass spectrometer.

EXAMPLE

The follow example is intended as illustrative and non-limiting, and

15 represents a specific embodiment of the present invention.

The present invention was used to study the catalytic formation of aniline. The reaction was carried out in a multi-well reactor of the type shown in Fig. 3. One hundred microliters of a 0.0128 M solution of ammonia dissolved in benzene was charged to each of the wells, along with a catalyst comprising an oxide of either

20 nickel, iron, or cobalt. Ammonia and benzene were allowed to react at 300 °C for four hours. Following reaction, fluid samples from each of the reaction mixtures were contacted with a silica gel sorbent to trap aniline present in the reaction mixtures. The silica gel was supplied on a TLC plate.

Two methods were used to contact the sorbent with fluid samples from each

25 of the reaction mixtures. In one method, 2 microliter aliquots from each of the reaction mixtures were spotted on the TLC plate using a pipette. In another method, the TLC plate was placed on the surface of the multi-well reactor. The reactor block was maintained at a temperature of 45 °C for 15 minutes, which completely vaporized (evaporated) the reaction mixtures, and allowed vapor from each of the

30 reaction mixtures to contact discrete areas of the silica gel layer.

For both contacting methods, an indicator reagent, fluorescamine (10-phenylspiro[2,3,3a,7a-tetrahydroindene-1,4'-cyclopentene]-10-ene) was used to detect aniline trapped on the silica gel layer. A 150 ppm solution of fluorescamine dispersed in methylene chloride was sprayed on the TLC plates using a commercially-available TLC aerosol applicator. The reaction between aniline and fluorescamine occurred in about twenty seconds at room temperature. The fluorescent product formed had a persistent fluorescence that was detected using long wavelength ultraviolet excitation energy (390 nm); the resulting fluorescence signal (490 nm) was passed through a blue-green filter and collected using a CCD camera. A photograph of the TLC plate spotted with 2 microliter aliquots of the reaction mixtures and stained with fluorescamine is shown in Fig. 7.

The fluorescent spots on the TLC plates were numerically integrated; a typical bar plot 280 of the integration data are shown in Fig. 8. Integrated fluorescence intensity for aniline standards trapped on the TLC plate along with aniline from the reaction mixtures is shown in the back row 282 of Fig. 8. Although the amount of aniline in the standards was apparently greater than the amount of aniline present in the reaction mixtures, normally the standards could be used to relate the fluorescence intensity to amount of aniline in the reaction mixtures.

In a separate experiment, aniline standards were applied to a TLC plate and detected in a manner identical to the reaction mixtures. Integration of the fluorescence signal from the standards indicates that the method is capable of detecting on the order of 0.5 ng of aniline, and that the linear dynamic range for detection extends over three orders of magnitude. See Fig. 9. Since fluorescamine is not fluorescent, it can be applied in large excess without interfering with the detection of aniline.

It is to be understood that the above description is intended to be illustrative and not restrictive. Many embodiments will be apparent to those of skill in the art upon reading the above description. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the appended claims, along with the full scope of

equivalents to which such claims are entitled. The disclosures of all articles and references, including patent applications and publications, are incorporated herein by reference for all purposes.

WHAT IS CLAIMED IS:

1. A method of analyzing reaction mixtures comprising the steps of:
contacting a fluid sample from one of the reaction mixtures with a sorbent;
trapping at least one component of the fluid sample on the sorbent; and
detecting the at least one component of the fluid sample trapped on the
sorbent;
wherein the contacting step, the trapping step, and the detecting step are
carried out at least once for each of the reaction mixtures.
2. The method of claim 1, wherein the at least one component is a reaction
product.
3. The method of claim 1, wherein the contacting step is carried out for at least
two of the reaction mixtures simultaneously.
4. The method of claim 1, wherein the detecting step is carried out for the at
least two of the reaction mixtures simultaneously.
5. The method of claim 1, wherein the fluid sample from each of the reaction
mixtures is in contact with the sorbent for about the same amount of time.
6. The method of claim 1, wherein the fluid sample in the contacting step is a
vapor.
7. The method of claim 6, wherein the contacting step further comprises the
step of vaporizing a portion of each of the reaction mixtures.
8. The method of claim 7, wherein the vaporizing step comprises heating each
of the reaction mixtures.
9. The method of claim 6, further comprising the steps of:
confining the reaction mixtures in wells formed in a surface of a reaction
block; and
disposing a layer of the sorbent on the surface of the reaction block, so that
the vapor from each of the reaction mixtures contacts discrete areas of
the layer during the contacting step.

10. The method of claim 9, wherein the layer of the sorbent is supported on a solid layer.
11. The method of claim 10, wherein the solid layer is gas permeable.
12. The method of claim 11, wherein the contacting step further comprises the steps of:
pressurizing at least one of the wells; and
venting the vapor from the at least one of the wells through the solid layer.
13. The method of claim 10, wherein the layer of the sorbent on the solid layer is discontinuous.
14. The method of claim 6, further comprising the steps of:
confining the reaction mixtures in vessels; and
providing fluid communication between the vapor from each of the reaction mixtures and the sorbent.
15. The method of claim 14, further comprising the step of placing the sorbent in one end of each of the vessels, so that the vapor from each of the reaction mixtures contacts the sorbent during the contacting step.
16. The method of claim 14, wherein the contacting step further comprises the steps of:
pressurizing at least one of the vessels; and
venting at least one of the vessels so that the vapor flows through the sorbent.
17. The method of claim 1, wherein the fluid sample in the contacting step is a liquid.
18. The method of claim 17, wherein the contacting step further comprises the steps of:
withdrawing a predetermined amount of the fluid sample from one of the reaction mixtures; and
applying the predetermined amount of the fluid sample on the sorbent.
19. The method of claim 1, wherein the detecting step further comprises the step of obtaining an absorption spectrum of the sorbent in order to detect the presence of the at least one component trapped on the sorbent.

20. The method of claim 19, wherein the absorption spectrum is obtained from an infrared region of the spectrum, an ultraviolet region of the spectrum, or a visible region of the spectrum.
21. The method of claim 1, wherein the detecting step further comprises the step of obtaining a nuclear magnetic resonance spectrum of the sorbent in order to detect the presence of the at least one component trapped on the sorbent.
22. The method of claim 1, wherein the detecting step further comprises the steps of:
removing the at least one component trapped on the sorbent; and
identifying the at least one component removed from the sorbent by gas chromatography, liquid chromatography, mass spectroscopy, nuclear magnetic resonance spectroscopy, or absorption spectroscopy.
23. The method of claim 22, wherein the removing step further comprises the step of heating the sorbent.
24. The method of claim 23, wherein the removing step further comprises the step of washing the sorbent with a solvent.
25. The method of claim 1, wherein the detecting step further comprises the steps of:
exposing the sorbent to an indicator reagent; and
observing a change in appearance of the sorbent resulting from an interaction of the indicator reagent with the at least one component.
26. The method of claim 25, wherein the interaction of the indicator reagent with the at least one component results in a change in color of the sorbent.
27. The method of claim 25, wherein the detecting step further comprises the step of irradiating the sorbent with ultraviolet light;
wherein the interaction of the indicator reagent with the at least one component results in a change in fluorescence of the sorbent during exposure to the ultraviolet light.
28. The method of claim 25, wherein the observing step further comprises the steps of:

obtaining a signal that is a measure of the appearance of the sorbent; and
comparing the signal to a calibration curve that relates the signal to an
amount of the at least one component trapped on the sorbent.

29. The method of claim 25, wherein the observing step comprises the steps of:
obtaining a first signal that is a measure of the appearance of the sorbent
resulting from the interaction of the indicator reagent with the at least
one component; and
comparing the first signal to a second signal that is a measure of the
appearance of the sorbent resulting from the interaction of the reagent
with a known amount of the at least one component.

30. A method of screening a group of catalysts comprising the steps of:
combining each of the catalysts with at least one reactant so as to form a plurality of reaction mixtures;
contacting a fluid sample from one of the reaction mixtures with a sorbent;
trapping at least one component of the fluid sample on the sorbent; and
detecting the at least one component of the fluid sample on the sorbent;
wherein the contacting step, the trapping step, and the detecting step are carried out at least once for each of the reaction mixtures.
31. The method of claim 30, wherein the at least one component is a reaction product.
32. The method of claim 30, wherein the combining step is carried out for at least two of the reaction mixtures simultaneously.
33. The method of claim 30, wherein the contacting step is carried out for at least two of the reaction mixtures simultaneously.
34. The method of claim 30, wherein the detecting step is carried out for at least two of the reaction mixtures simultaneously.
35. The method of claim 30, wherein the fluid sample from each of the reaction mixtures is in contact with the sorbent for about the same amount of time.
36. The method of claim 30, wherein the at least one reactant is the same for each of the reaction mixtures formed in the combining step.
37. The method of claim 30, wherein the fluid sample in the contacting step is a vapor.
38. The method of claim 37, wherein the contacting step further comprises the step of vaporizing a portion of each of the reaction mixtures.
39. The method of claim 38, wherein the vaporizing step comprises heating each of the reaction mixtures.
40. The method of claim 37, wherein the combining step further comprises the step of confining each of the catalysts and the at least one reactant in wells formed in a surface of a reaction block so as to form the plurality of reaction mixtures.

41. The method of claim 40, further comprising the step of disposing a layer of the sorbent on the surface of the reaction block, so that the vapor from each of the reaction mixtures contacts discrete areas of the layer during the contacting step.
42. The method of claim 41, wherein the layer of the sorbent is supported on a solid layer.
43. The method of claim 42, wherein the solid layer is gas permeable.
44. The method of claim 43, wherein the contacting step further comprises the steps of:
pressurizing at least one of the wells; and
venting the vapor from the at least one of the wells through the solid layer.
45. The method of claim 42, wherein the layer of the sorbent on the solid layer is discontinuous.
46. The method of claim 37, wherein the combining step further comprises the steps of:
confining each of the catalysts and the at least one reactant in vessels so as to
form the plurality of reaction mixtures; and
providing fluid communication between the vapor from each of the reaction mixtures and the sorbent.
47. The method of claim 46, further comprising the step of placing the sorbent in one end of each of the vessels, so that the vapor from each of the reaction mixtures contacts the sorbent during the contacting step.
48. The method of claim 46, wherein the contacting step further comprises the steps of:
pressurizing at least one of the vessels; and
venting the at least one of the vessels so that the vapor from each of the reaction mixtures flows through the sorbent.
49. The method of claim 30, wherein the fluid sample in the contacting step is a liquid.

50. The method of claim 49, wherein the contacting step further comprises the steps of:
withdrawing a predetermined amount of the fluid sample from one of the
reaction mixtures; and
applying the predetermined amount of the fluid sample on the sorbent.
51. The method of claim 30, wherein the detecting step further comprises the step of obtaining an absorption spectrum of the sorbent in order to detect the presence of the at least one component trapped on the sorbent.
52. The method of claim 51, wherein the absorption spectrum is obtained from an infrared region of the spectrum, an ultraviolet region of the spectrum, or a visible region of the spectrum.
53. The method of claim 30, wherein the detecting step further comprises the step of obtaining a nuclear magnetic resonance spectrum of the sorbent in order to detect the presence of the at least one component trapped on the sorbent.
54. The method of claim 30, wherein the detecting step further comprises the steps of:
removing the at least one component trapped on the sorbent; and
identifying the at least one component removed from the sorbent by gas chromatography, liquid chromatography, mass spectrometry, nuclear magnetic resonance spectrometry, or absorption spectrometry.
55. The method of claim 54, wherein the removing step further comprises the step of heating the sorbent.
56. The method of claim 54, wherein the removing step further comprises the step of washing the sorbent with a solvent.
57. The method of claim 30, wherein the detecting step further comprises the steps of:
exposing the sorbent to an indicator reagent; and
observing a change in appearance of the sorbent resulting from an interaction of the indicator reagent with the at least one component.

58. The method of claim 57, wherein the interaction of the indicator reagent with the at least one component results in a change in color of the sorbent.
59. The method of claim 57, wherein the detecting step further comprises the step of irradiating the sorbent with ultraviolet light;
wherein the interaction of the indicator reagent with the at least one component results in a change in fluorescence of the sorbent during exposure to the ultraviolet light.
60. The method of claim 57, wherein the observing step further comprises the steps of:
obtaining a signal that is a measure of the appearance of the sorbent; and
comparing the signal to a calibration curve that relates the signal to an amount of the at least one component trapped on the sorbent.
61. The method of claim 57, wherein the observing step comprises the steps of:
obtaining a first signal that is a measure of the appearance of the sorbent resulting from the interaction of the indicator reagent with the at least one component; and
comparing the first signal to a second signal that is a measure of the appearance of the sorbent resulting from the interaction of the reagent with a known amount of the at least one component.

62. An apparatus for analyzing reaction mixtures comprising:
a reaction block having wells formed along an upper surface;
a sorbent layer disposed above the upper surface of the reaction block such
that the wells and the sorbent layer define vessels for containing the
reaction mixtures;
wherein the sorbent layer is adapted to trap at least one fluid component of
the reaction mixtures.
63. The apparatus of claim 62, wherein the reaction block further comprises
heating elements.
64. The apparatus of claim 62, wherein the reaction block further comprises a
system for regulating temperature of the reaction mixtures.
65. The apparatus of claim 62, wherein the wells each contain a removable
lining.
66. The apparatus of claim 62, wherein the sorbent layer is supported on a solid
layer.
67. The apparatus of claim 66, wherein the sorbent layer and the solid layer
comprise a thin layer chromatography plate.
68. The apparatus of claim 66, wherein the solid layer is gas permeable.
69. The apparatus of claim 68, further comprising a cover having an upper
surface and a lower surface, the lower surface of the cover disposed above
the solid layer; and
a plurality of conduits formed in the cover that provide passageways for
vapor flow between each of the vessels and the upper surface of the
cover.

70. An apparatus for analyzing reaction mixtures comprising:
vessels for containing each of the reaction mixtures; and
sorbent traps in fluid communication with the vessels;
wherein the sorbent traps are adapted to trap at least one fluid component of
the reaction mixtures.
71. The apparatus of claim 70, further comprising:
a reaction block having wells formed along an upper surface; and
a cover having an upper surface and a lower surface;
wherein the cover is disposed above the upper surface of the reaction block
such that the wells and the lower surface of the cover define the
vessels for containing each of the reaction mixtures.
72. The apparatus of claim 71, wherein each of the vessels contain a removable
lining.
73. The apparatus of claim 71, wherein the sorbent traps are located in the
vessels adjacent to the lower surface of the cover.
74. The apparatus of claim 71, further comprising passageways formed in the
cover that extend from the lower surface of the cover to the upper surface of
the reaction cover.
75. The apparatus of claim 74, wherein the sorbent traps are located in at least
some of the passageways.
76. The apparatus of claim 74, wherein the passageways further comprise inlet
passageways and outlet passageways, wherein the outlet passageways contain
the sorbent traps and the inlet passageways are adapted to provide a
component of the reaction mixtures to each of the vessels.
77. The apparatus of claim 74, wherein the sorbent traps are located external to
the cover and communicate with the vessels through the passageways.
78. The apparatus of claim 74, wherein the passageways further comprise inlet
passageways and outlet passageways, wherein the sorbent traps communicate
with the vessels through the outlet passageways, and the inlet passageways

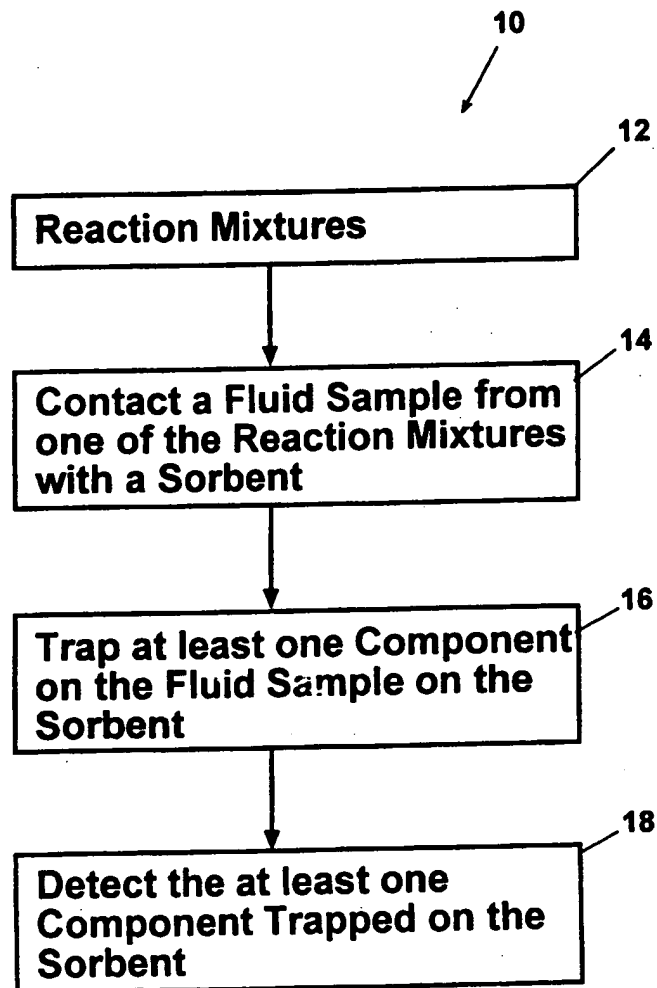
are adapted to provide a component of the reaction mixtures to each of the vessels.

79. The apparatus of claim 70, further comprising heating elements in thermal contact with the vessels.
80. The apparatus of claim 70, further comprising a temperature control system for regulating the temperature of the reaction mixtures.

81. An apparatus for screening reaction mixtures, wherein at least one constituent of the reaction mixtures is contained in depressions located along a top surface of a planar substrate, the apparatus comprising:
a heating block adapted to support the planar substrate and to provide thermal contact with a bottom surface of the planar substrate;
a gas permeable sorbent layer having an upper surface and a lower surface, wherein the lower surface of the sorbent layer is disposed above the top surface of the planar substrate, and the sorbent layer is adapted to trap at least one vapor phase component of the reaction mixtures;
a cover having an upper surface and a lower surface, the lower surface of the reactor cover disposed above the upper surface of the sorbent layer;
and
passageways formed in the cover that extend from the lower surface of the cover to the upper surface of the cover and provide flow paths for vapor phase components of the reaction mixtures from the upper surface of the cover to the at least one constituent of the reactive mixture.
82. The apparatus of claim 81, wherein the heating block further comprises a system for regulating temperature of the reaction mixtures.
83. The apparatus of claim 81 further comprising a gas permeable solid layer having an upper surface and a lower surface, wherein the sorbent layer is supported on one of the upper surface of the gas permeable solid layer and the lower surface of the gas permeable solid layer.
84. The apparatus of claim 83, wherein the solid layer is a frit, quartz paper, or a wire mesh.
85. The apparatus of claim 84, wherein the frit is made of glass, polyethylene, or polytetrafluoroethylene.
86. The apparatus of claim 83, wherein the sorbent layer is discontinuous.

87. The apparatus of claim 86, wherein the sorbent layer is disposed in depressions formed along one of the upper surface of the gas permeable solid layer and the lower surface of the gas permeable solid layer.

1/8

**Fig. 1**

2/8

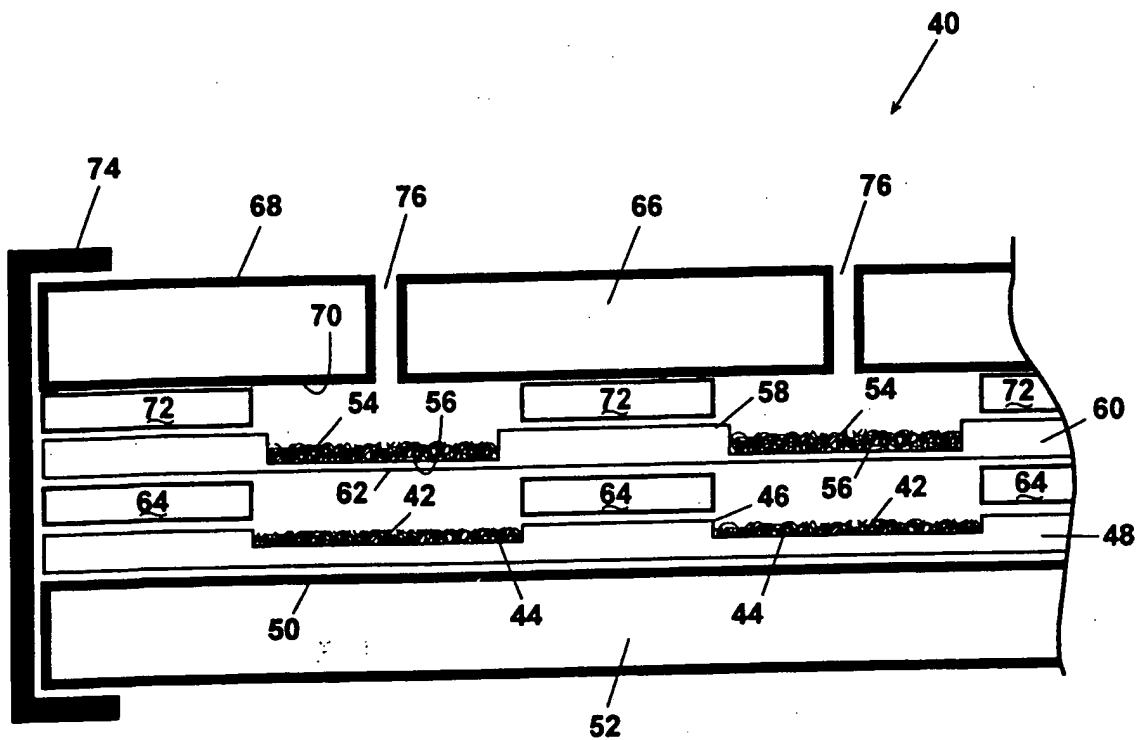


Fig. 2

3/8

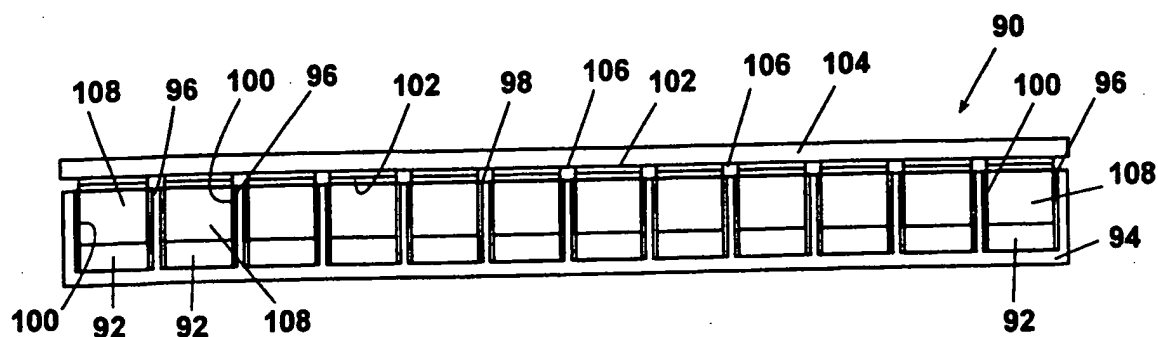


Fig. 3

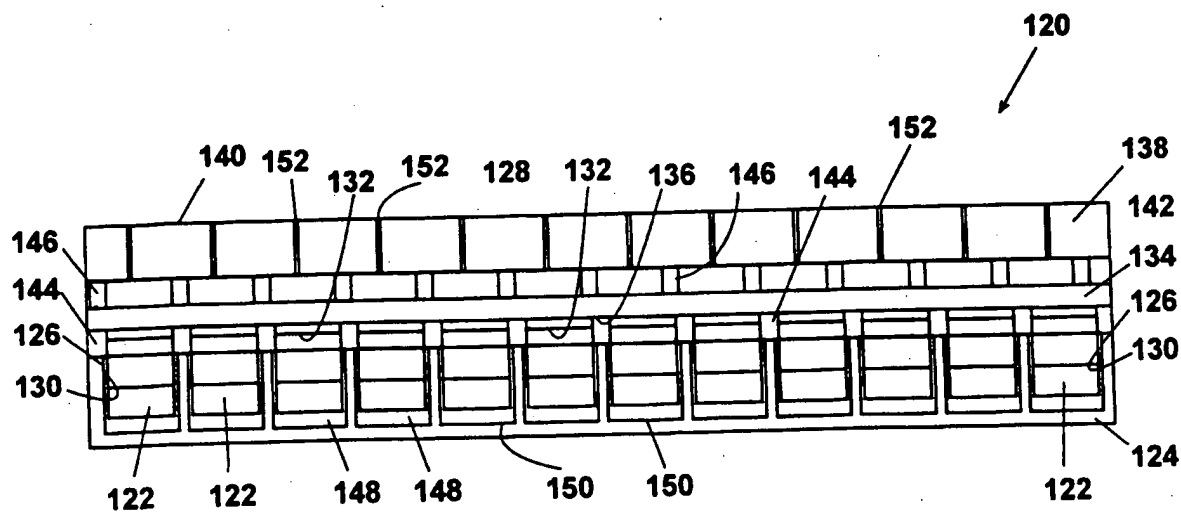


Fig. 4

4/8

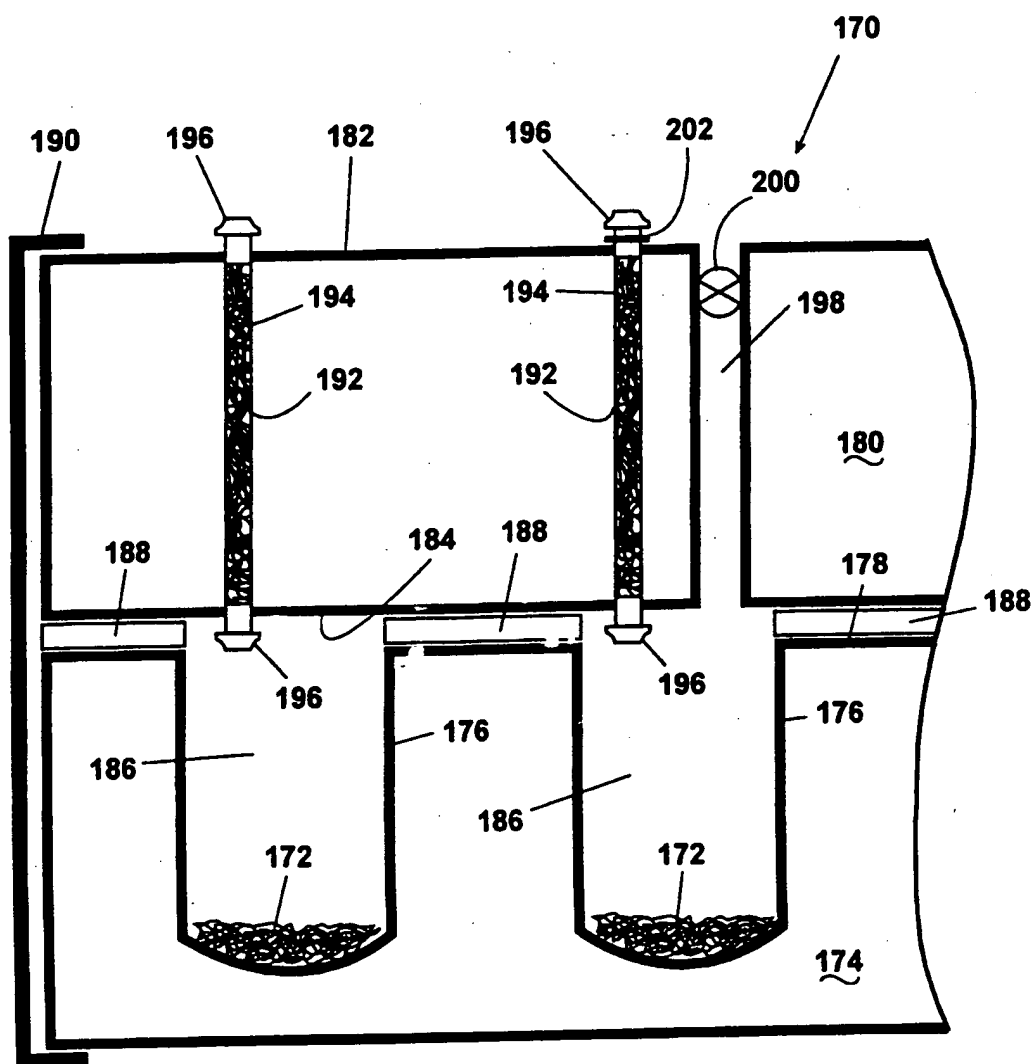


Fig. 5

5/8

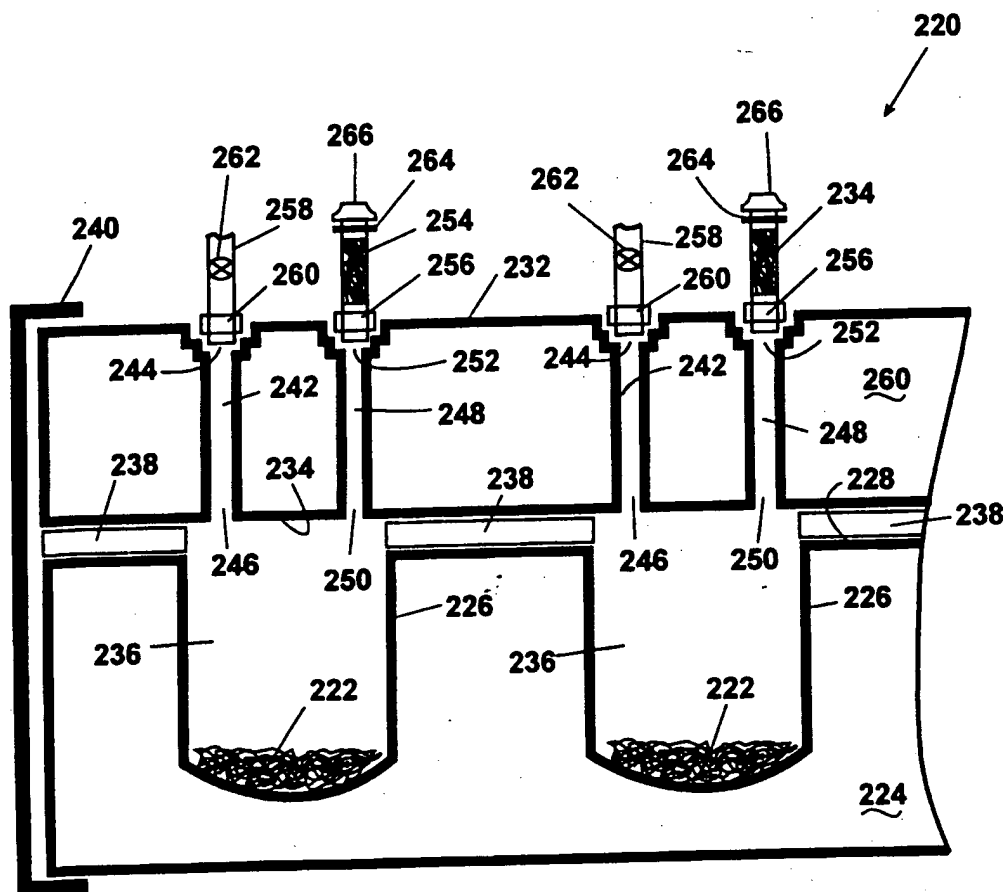


Fig. 6

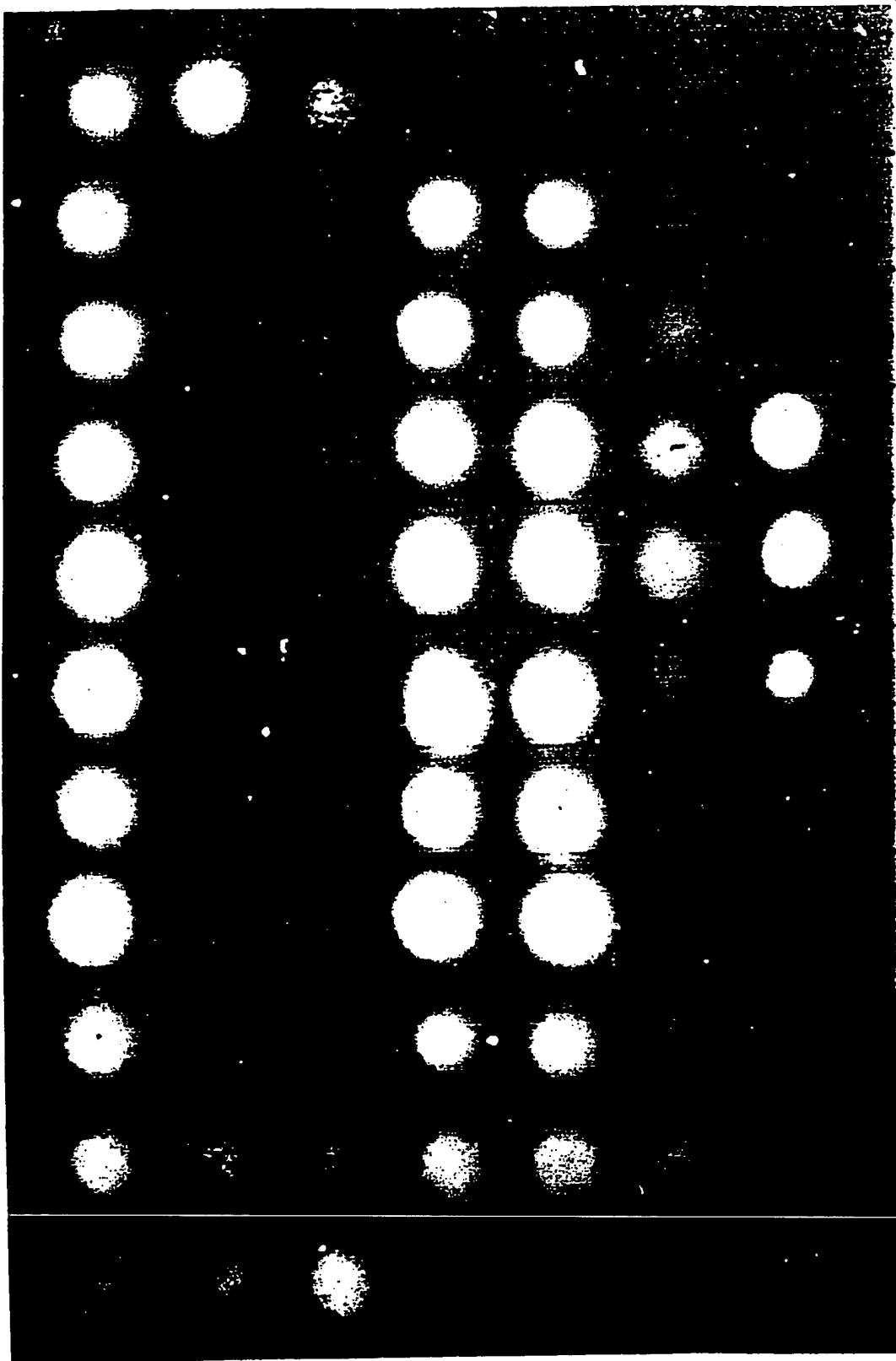


FIG. 7

7/8

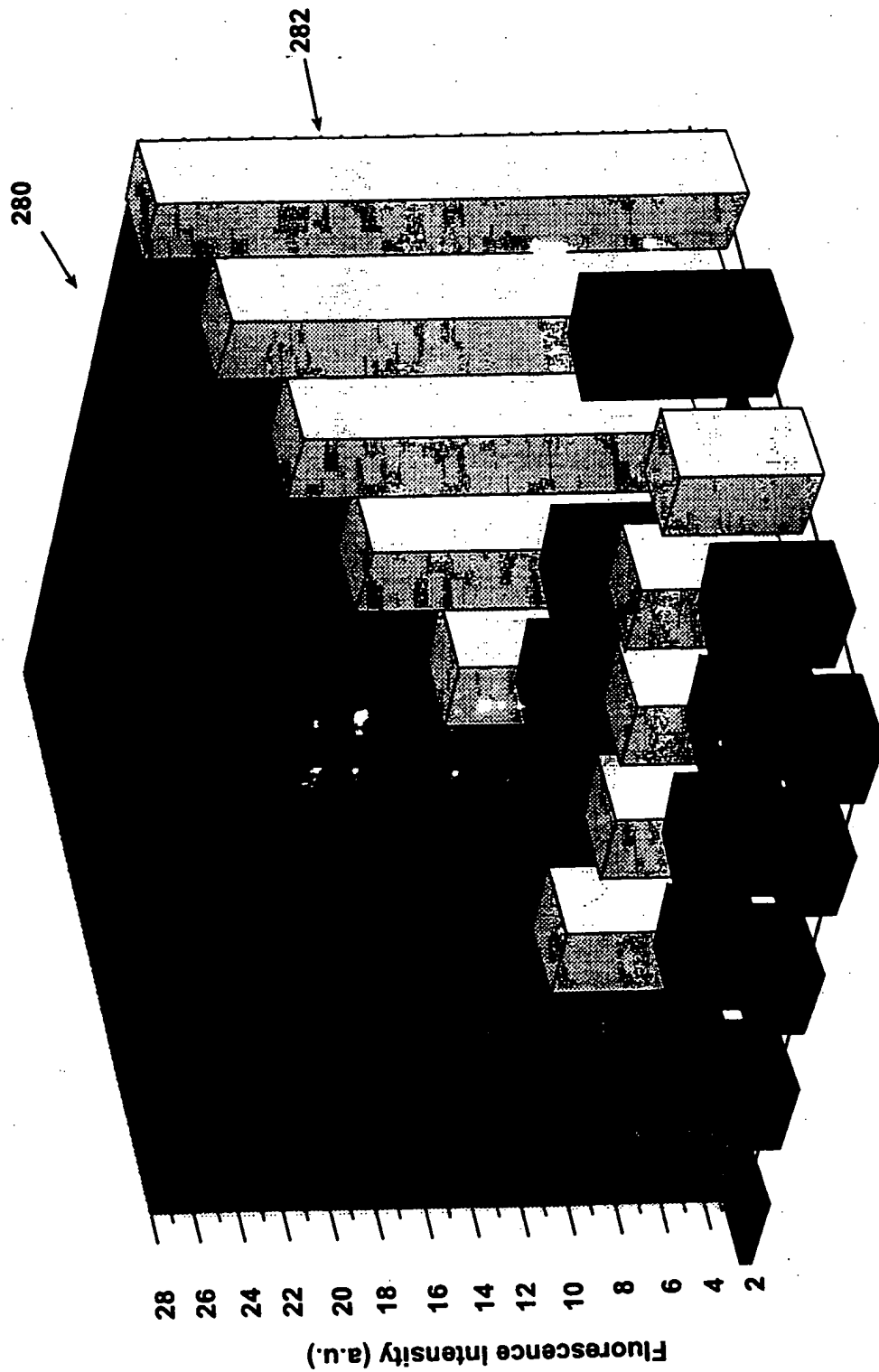
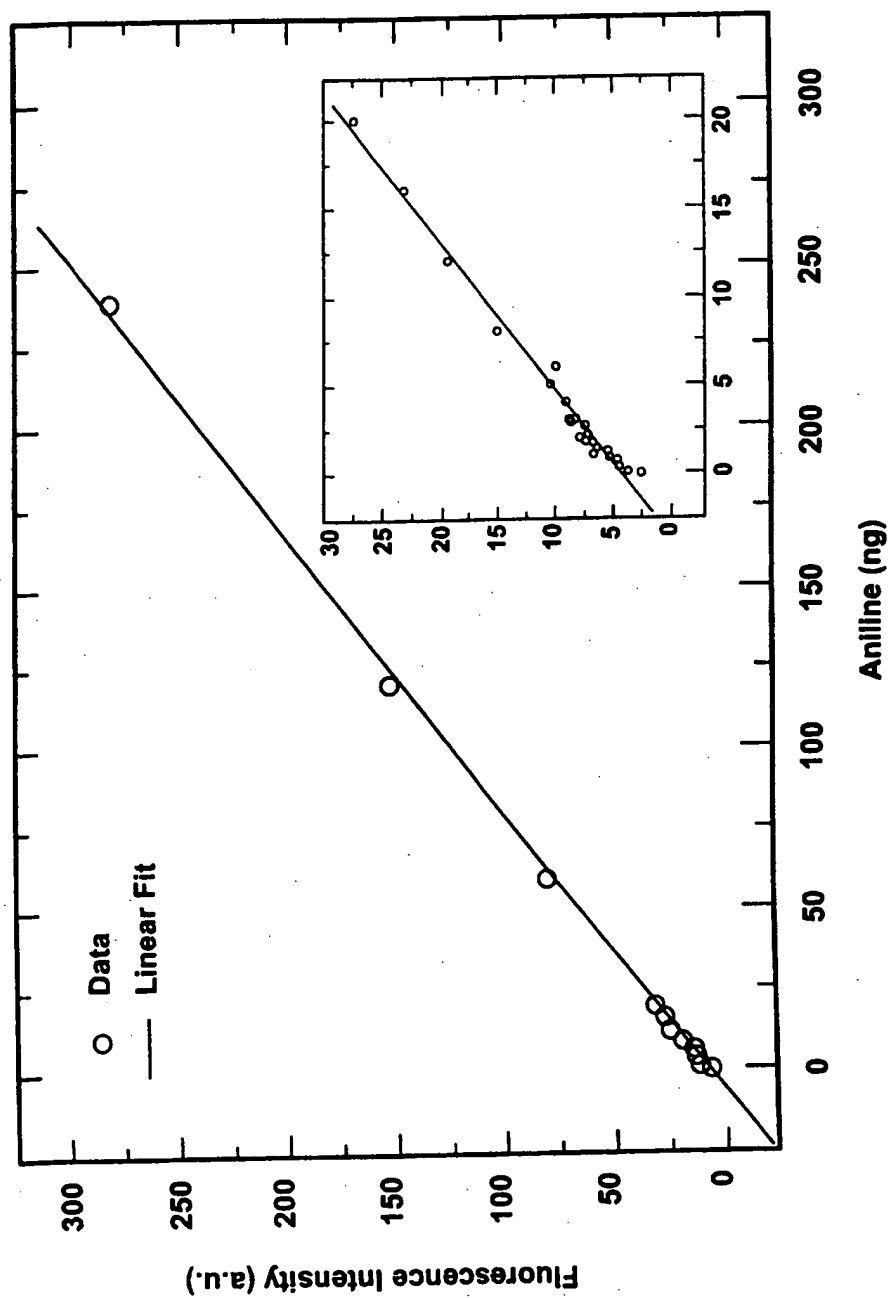


Fig. 8

**Fig. 9**

INTERNATIONAL SEARCH REPORT

Intern: 11 Application No

PCT/US 99/20380

A. CLASSIFICATION OF SUBJECT MATTER

G01N31/02, G01N33/00, B01J19/00

According to International Patent Classification (IPC) or to both national classification and IPC 7

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

G01N, B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 98/56796 A (SYMYX TECHNOLOGIES) 17 December 1998, the whole document. --	1-87
X, P	WO 99/05318 A (SYMYX TECHNOLOGIES) 04 February 1999, the whole document. --	1-87
A	WO 98/03521 A (SYMYX TECHNOLOGIES) 29 January 1998, the whole document (cited in the application). ----	1-87

☐

Further documents are listed in the continuation of box C.

☐

Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

12 December 1999

Date of mailing of the international search report

25. 02. 2000

Name and mailing address of the ISA

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Authorized officer

TENGLER e.h.

ANHANG

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

ANNEX

To the International Search Report to the international Patent Application No.

PCT/US 99/20380 SAE 249582

This annex lists the patent family members relating to the patent documents cited in the above-mentioned search report. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

ANNEXE

Au rapport de recherche international relatif à la demande de brevet international n°

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visés ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office.

Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9856796	17-12-1998	AU A1 78016/98	30-12-1998
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